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| 10/701,331 | 11/04/2003 | Douglas B. Cines | UPN-O2906AUSA | 5594 |

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| KAUSHAL, SUMESH | |
| **ART UNIT** | **PAPER NUMBER** |
| 1633 | |

DATE MAILED: 04/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/701,331 | CINES ET AL. | |
| | Examiner | Art Unit | |
| | Sumesh Kaushal Ph.D. | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *11-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 19-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's response filed on 2/10/06 has been acknowledged.

*Claims 1-35 are pending and are examined in this office action.*
*Claims 11-18 are withdrawn by the applicant.*

*Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is* ***571-273-8300.***

### *Election/Restrictions*

Applicant's election with traverse of Group I (Claims 9-10, 22 and 33-35) in the reply filed on 2/10/06 is acknowledged. Claims 1-8, 19-21 and 23-32 are generic. The traversal is on the ground(s) that election of species in claims 3, 4, 5 7, 10, 12, 16, 21 and 34 encompasses members that are sufficiently few in number or are closely related that search and examination of entire claim can be made without serious search burden. This is not found persuasive because the recombinant nucleic acid sequences claims 3, 4, 5 7, 10, 12, 16, 21 and 34 encompasses species that are structurally and functionally distinct sequences, therefore are not closely related as search of one would not lead to other. Thus there exists a serious search burden to search and examine entire claims.

The requirement is still deemed proper and is therefore made FINAL.

Claims 11-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/10/06.

### *Claim Objections*

Claims 3, 4, 5, 7, 10, 12, 16, 21 and 34 objected to because of the following informalities: The instant claims recite non-elected subject matter. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 19-33 and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The scope of invention as claimed encompasses a recombinant nucleic acid molecule (or use thereof) comprising a transgene under the control of a regulatory sequence that directs the expression of the transgene in a hematopoietic stem cell progenitor cell or a cell differentiated therefrom (see claim 1, 23, 26). The scope of invention as claimed further encompasses a platelet transformed with a recombinant nucleic acid molecule comprising a transgene under the control of a regulatory sequence that directs the expression of the transgene in the platelets (see claim 22). The scope of invention as claimed encompasses method of treating or preventing thrombus formation in a mammal by using a recombinant nucleic acid molecule comprising a transgene encoding a fibronolytic protein under the control of a regulatory sequence that directs the expression of the transgene in platelets. At best the specification teaches a recombinant nucleic acid molecule comprising u-PA transgene under the control of PF4 promoter that directs the expression of the transgene in platelets (see fig-1). The specification fail to disclose any other recombinant molecule comprising a transgene under the control of a regulatory sequence that directs the expression of the transgene in a hematopoietic stem cell progenitor cell or a cell differentiated therefrom especially platlets.

Applicant is referred to the guidelines for ***Written Description Requirement*** published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110 (see http://www.uspto.gov). The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In analyzing whether the written description requirement is met for the genus claim, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e conserve motifs or domains).

The specification fails to disclose representative number of species defined by structure and function that ate encompassed by genus as claimed. Furthermore the genus as claimed encompasses structurally and functionally distinct members. Claiming all divergent species that achieve a result as contemplated by the application without defining the representative number of species by structure and function is not in compliance with the written description requirement, rather, it is an attempt to preempt the future before it has arrived. "The written description requirement has several policy objectives. The essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." In re Barker, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. See Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1566, 43USPQ2d 1398, 1404 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998)." To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to

practice, showing that the invention as claimed is "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention (January 5, 2001 Fed.Reg., Vo.66, No. 4, pp. 1099-11).

Since the specification fails to disclose a representative number of species defined by structure and function, it is not possible to envision the claimed composition. One cannot describe what one has not conceived. (See Fiddes v. Baird, 30 USP2d 1481 at 1483). Therefore, the lack of disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the applicants were in possessions of the huge genera recited in the claims at the time the application was filed. Furthermore the possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568; 43 USPQ2d at 1406).* In the instant case the nucleic acid sequences as claimed has been defined only by a statement of function that broadly encompasses a regulatory sequence that directs the expression of the transgene in a hematopoietic stem cell progenitor cell or a cell differentiated therefrom especially platelets like activity; or any fibronolytic protein like activity which conveyed no distinguishing information about the identity of the claimed

genetic material, such as its relevant structural or physical characteristics. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of even a single member of this genus would not be representative of other nucleic acid constructs genus and is insufficient to support the claim.

Claims 1-10 and 19-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant nucleic acid molecule comprising the u-PA transgene under the control of PF4 promoter that directs the expression of the transgene in platelets, does not reasonably provide enablement for a recombinant nucleic acid molecule (or use thereof) comprising a transgene under the control of any regulatory sequence that directs the expression of the transgene in any hematopoietic stem cell, any progenitor cell or any cell differentiated therefrom. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Since the specification fails to disclose a representative number of species defined by structure and function, it is unclear how one skilled in the art use the invention as claimed (supra). The applicant's disclosure does not enable one skilled in the art to practice the invention as claimed without further undue amount of experimentation, which requires the identification and characterization of any and all regulatory sequences that directs the expression of the transgene in any hematopoietic stem cell, any progenitor cell or any cell differentiated therefrom. At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In addition it is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may

not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

Claims 26-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

**Nature Of Invention**

The instant invention relates to a metod for gne therapy.

**Breadth Of Claims And Guidance Provided in the Specification**

The invention as claimed is drawn to a method of treating any disorder in a mammal by delivering a recombinant nucleic acid comprising any transgene under the control of any regulatory sequence that directs the expression of the transgene product in a hematopoietic stem cell progenitor cell or a cell differentiated therefrom. The scope of invention as claimed further encompasses a method for treating or preventing thrombus formation induced by any etiological factor in a mammal by delivering to the mammal a recombinant nucleic acid molecule comprising any fibrinolytic-transgene under the control of any regulatory sequence that directs the expression of the transgene product in a platelet. At best the specification teaches transgenic mice expressing u-PA under the control of PF4 promoter region. Using the u-PA-transgenic-mouse model the specification teaches a Ferric-chloride-induced carotid artery thrombosis model suggesting that few transgenic animals expressing u-PA formed

completely occlusive coronary thrombi after ferric chloride induced injury (spec. para. 0152, and table-1). However, the specification as filed fails to provides any evidence that would enable one skilled in the art to treat and/or prevent any disorder especially thrombus formation via a method of gene therapy as claimed herein.

**State Of Art And Predictability**

The scope of the instant invention encompasses genetic modification of a cell in-vivo, therefore the invention falls in the realm of gene therapy. The gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations (see Goncalves, Bioessays. 27(5):506-517, 2005; Juengst, BMJ, 326:1410-11, 2003; Couzin et al, SCIENCE 307:1028, 2005; Rosenberg et al, SCIENCE 287:1751, 2000; Anderson, NATURE 392:25-30, 1998; Touchette, NAT. MED. 2(1) 7-8, 1996). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success. The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease.

In instant case the invention as claimed intend to treat an overly broad genus of disorders using overly broad genus of therapeutic transgene, which does not enable one skilled in the art to practice the invention as claimed without further undue amount of experimentation that would require the understanding of an underlying mechanism any and all disorders in context to any and all therapeutic transgenes. It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly

need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

Furthermore, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors. Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. On the other hand vector comprising DNA viruses and liposome coated DNA have been used to transduce non dividing cells but this results in a transient expression due to non-integration of transgenes in host cells. In addition, the use of adenoviral and adeno associated viral vector is also problematic because these vectors elicits considerable immune response in vivo, which affects the sustained expression of the transduced genes. Furthermore, in vitro gene transfer studies are not predictive of in-vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in-vivo environment. Similarly transgenic animal models does not represent the product and protocols required for the method of gene therapy. In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacles to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets. In addition there exists an uncertainty about the degree to which a vector's genetic material may integrate into the host genome extends to most types of gene therapy trials. Scientists are also unsure how an insertion could affect a patient, and worry cancer could occasionally be triggered, such as occurred various trials involving gene therapy (see Check Nature 422:7, 2003). Although, the gene therapy holds much promise to come, the success will only be achieved through continued rigorous research on the most fundamental mechanisms that contribute to a

genetic disease along with the pathogenesis of the disease, gene delivery and gene expression in animals.

Considering the unpredictability in the state of art the specification as filed fails to provide any evidence that delivery of a recombinant vector (viral or non-viral) via any and all route of administration (oral, nasal, local or systemic etc.) that encodes any fibrinolytic-protetin (especially u-PA) results in the treatment or prevention of any disorder (like thrombus) in a mammal. At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In instant case gene based therapy to treat any disorder using any gene of interest is not considered routine in the art and without sufficient guidance to a specific therapeutic gene and its successful delivery to targeted tissue the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-10, 19-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Rosenberg et al (WO 92/06190, 1992).

Regarding the nucleic acid sequences as claimed in claims 1-10, the cited art teaches a recombinant expression vector comprising PF4 operably linked to Lac Z transgene (see fig-2A). Regarding the host cells as claimed in claims 19-25 the cited art teaches genetically modified hematopoietic bone marrow cells and platelet that contains exogenous PF4 operably linked to Lac Z transgene (page 6, line 4-11, page 44, lines 22-29, page 46-47, fig 2, fig-3). Thus the cited art clearly anticipate the invention as claimed.

***Conclusion***

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

- **US Pat No. 5,489,743, 1996.**
- Ravid et al, Targeted expression of a conditional oncogene in hematopoietic cells of transgenic mice. **J Cell Biol. 123(6 Pt 1):1545-53. 1993.**
- Ravid et al, Selective targeting of gene products with the megakaryocyte platelet factor 4 promoter. **Proc Natl Acad Sci U S A. 88(4):1521-5, 1991.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**

**SUMESH KAUSHAL**
**PRIMARY EXAMINER**
**ART UNIT 1633**